EXHIBIT 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Tutino *et al.*	Confirmation No.: 6628
Application No.: 12/783,390	Group Art Unit: 1617
Filed: May 19, 2010	Examiner: Pipic, Alma
For: Formulations of 4-Amino-2-(2,6-Dioxopiperidine-3-yl) isoindoline-1,3-dione	Attorney Docket No.: 9516-831-999 CAM: 501872-999831

AMENDMENT AND RESPONSE

Mail Stop Amendment
Commissioner for Patents
PO BOX 1450
Alexandria, Virginia 22313-1450

Sir:

In response to the Office Action mailed April 24, 2012, please consider the following amendments and remarks in connection with the above-identified application.

An extension of time for a period of one month, the fee for which will be paid via EFS-Web, is respectfully requested herein.

Amendments to the Specification are reflected on page 2 of this paper.

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 3 of this paper.

Remarks begin on page 7 of this paper.

AMENDMENTS TO THE SPECIFICATION:

Please replace the current specification with the substitute specification attached hereto. The only amendments made in the substitute specification are replacement of the term "pomolidomide"with "pomalidomide" and thus, the substitute specification contains no new matter. A marked-up version of the current specification, showing these amendments, is also attached hereto.

LISTING OF CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently amended) An oral dosage form which weighs about 62.5 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 35 mg; 3) sodium stearyl fumarate at an amount of 0.16 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 62.5 mg.

2-9. (Canceled).

10. (Previously presented) The dosage form of claim 1, which is to be administered in the form of a size 4 or larger capsule.

11. (Currently Amended). An oral dosage form which weighs about 125 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 70 mg; 3) sodium stearyl fumarate at an amount of 0.32 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 125 mg.

12-19. (Canceled).

20. (Previously presented) The dosage form of claim 11, which is to be administered in the form of a size 4 or larger capsule.

21. (Currently amended) An oral dosage form which weighs about 250 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a~~

~~pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 140 mg; 3) sodium stearyl fumarate at an amount of 0.64 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 250 mg.

22-29. (Canceled)

30. (Previously presented) The dosage form of claim 21, which is to be administered in the form of a size 2 or larger capsule.

31. (Currently amended) An oral dosage form which weighs about 180 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 100.8 mg; 3) sodium stearyl fumarate at an amount of 0.45 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 180 mg.

40. (Previously presented) The dosage form of claim 31, which is to be administered in the form of a size 2 or larger capsule.

41. (Currently amended) An oral dosage form which weighs about 240 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 134.4 mg; 3) sodium stearyl fumarate at an amount of 0.6 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 240 mg.

42-49. (Canceled).

50. (Previously presented) The dosage form of claim 41, which is to be administered in the form of a size 2 or larger capsule.

51. (Currently amended) An oral dosage form which weighs about 300 mg and comprises: 1) ~~pomolidomide~~ pomalidomide, or a pharmaceutically acceptable salt or solvate thereof, at an amount that provides 1 mg potency of ~~pomolidomide~~ pomalidomide; ~~and 2) a pharmaceutically acceptable carrier or excipient~~ 2) pregelatinized starch at an amount of 168 mg; 3) sodium stearyl fumarate at an amount of 0.75 mg; and 4) spray dried mannitol at an amount that brings the total weight of the composition to 300 mg.

52-59. (Canceled)

60. (Previously presented) The dosage form of claim 51, which is to be administered in the form of a size 1 or larger capsule.

61. (New) An oral dosage form in the form of a capsule which comprises: 1) pomalidomide at an amount of 0.1 to 3 weight percent of the total weight of the composition; 2) a binder or filler at an amount of 90 to 99 weight percent of total weight of the composition, wherein the binder or filler is starch, mannitol or a mixture thereof.

62. (New) The oral dosage form of claim 61, wherein pomalidomide is present at an amount of 0.5 to 2 weight percent of total weight of the composition.

63. (New) The oral dosage form of claim 61, wherein the binder or filler is present at an amount of 95 to 99 weight percent of total weight of the composition.

64. (New) The oral dosage form of claim 61, wherein the binder or filler is a mixture of starch and mannitol.

65. (New) The oral dosage form of claim 64, wherein the starch is pregleatinized starch.

66. (New) The oral dosage form of claim 64, wherein the mannitol is spray dried mannitol.

67. (New) The oral dosage form of claim 61 further comprising a lubricant at an amount of 0.01 to 1 weight percent of total weight of the composition.

68. (New) The oral dosage form of claim 7, wherein the lubricant is present at an amount of 0.1 to 0.5 weight percent of total weight of the composition.

69. (New) The oral dosage form of claim 7 or 8, wherein the lubricant is sodium stearyl fumarate.

REMARKS

Upon entry of the specification and claim amendments presented herein, claims 1, 10, 11, 20, 21, 30, 31, 40, 41, 50, 51, and 60-69 are pending in the present application. Claims 2-9, 12-19, 22-29, 32-39, 42-49, and 52-59 are canceled without prejudice to Applicants' right to pursue any canceled subject matter in one or more divisional, continuation, and/or continuation-in-part applications. The specification and claims 1, 11, 21, 31, 41, and 51 are amended to replace all recitations of "pomolidomide" with "pomalidomide" solely to correct informalities alleged by the Examiner. Claims 1, 11, 21, 31, 41, and 51 are further amended to recite more precisely the compositions of the claimed oral dosage forms. Support for amended claim 1 can be found, for example, on page 10, lines 15-21 of the present specification. Support for amended claim 11 can be found, for example, on page 11, lines 5-11 of the present specification. Support for amended claim 21 can be found, for example, on page 11, line 30 to page 12, line 2 of the present specification. Support for amended claim 31 can be found, for example, on page 12, lines 21-27 of the present specification. Support for amended claim 41 can be found, for example, on page 13, lines 10-16 of the present specification. Support for amended claim 51 can be found, for example, on page 14, lines 1-7 of the present specification.

New claims 61-69 are added. Support for new claim 61 can be found at page 7, lines 26-29 of the present specification. Support for new claim 62 can be found at page 7, lines 31-34 of the present specification. Support for new claim 63 can be found at page 8, lines 20-22 of the present specification. Support for new claim 64 can be found at page 8, line 26 to page 9, line 2 of the present specification. Support for new claims 65-66 can be found at page 8, lines 9-13 of the present specification. Support for new claim 67 can be found at page 9, lines 6-9 of the present specification. Support for new claim 68 can be found at page 9, lines 14-16 of the present specification. Support for new claim 69 can be found at page 9, line 9 of the present specification. No new matter is added.

Applicants respectfully submit that all of the pending claims are allowable for at least the reasons set forth below.

A. The Objection to Claims 1, 11, 21, 31, 41, and 51 Should Be Withdrawn

Claims 1, 11, 21, 31, 41, and 51 are objected to because the claims recite "pomolidomide" rather than "pomalidomide." (Office Action, page 4). This error has been corrected by amendments to the claims and specification. Withdrawal of the objection is respectfully requested.

B. The Rejection Under 35 U.S.C. § 112, 2nd Paragraph Should be Withdrawn

On page 3 of the Office Action, claims 1-60 are rejected as allegedly indefinite. Specifically, the Examiner alleges that claims 1, 11, 21, 31, 41, and 51 are indefinite because "they recite potency of pomalidomide in milligrams. Potency of a drug is expressed in International Units (IU) and not mass." (Office Action, page 3). Applicants respectfully disagree and submit that the potency of pomalidomide, as recited by the pending claims, is unambiguously explained in the specification. For example, in page 9, lines 20-25 of the specification, it is provided that: "[i]n some embodiments, because it is typical to obtain pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, at a purity of less than 100%, the formulations and dosage forms provided herein may be defined as compositions, formulations, or dosage forms that comprise pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, at an amount that provides the potency of a specified amount of 100% pure pomalidomide." (Specification, page 9, line 27 to page 10, line 2). Based on this disclosure, those skilled in the art would clearly understand the meaning of this claim language. Accordingly, Applicants respectfully request that the Examiner's rejection be withdrawn.

C. The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

On pages 4-7 of the Office Action, claims 1-4, 7, 11-14, 17, 21-24, 27, 31-34, 37, 41-44, 47, 51-54 and 57 are rejected as allegedly obvious over Zeldis *et al.* U.S. Pub. No. 2007/1055791 ("Zeldis"). The Examiner alleges that "it would have been obvious to optimize the concentration of pomalidomide and excipients because the claimed ranges overlap with the ranges disclosed by Zeldis." (Office Action, page 5). Applicants respectfully disagree.

First, Applicants respectfully point out that even after the decision in *KSR*, Federal Circuit made it clear that to establish a *prima facie* case of obviousness of chemical compounds, a reason to select a "lead compound" and modify that compound, along with a reasonable expectation of

success, is still required. For example, in *Takeda chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, the Federal Circuit held that no *prima facie* case of obviousness existed with respect to a claimed compound, in part, because "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." (*Takeda*, 492 F.3d 1350, 1359 (Fed. Cir. 2007)). In *Takeda*, the skilled artisan was faced with a large list of antidiabetic compounds, but there was no teaching that would have made the compound of the claimed invention stand out over the other alternatives. (*Id.*). Moreover, a *prima facie* case of obviousness for a chemical compound "clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound." (*Id.* at 1359).

In view of the above, Applicants respectfully submit that although Zeldis may generally disclose a laundry list of compostions containing pomalidomide in combination with a broad range of possible excipients that may be used in such compositions, there is no disclosure in Zeldis that would have prompted one skilled in the art to prepare a composition having pomalidomide at the specified amounts, along with the particular binders and fillers at the specified amounts as recited by claims 1, 11, 21, 31, 41 and 51. Indeed, it is respectfully pointed out that, especially with regard to the excipients, there is no disclosure in Zeldis that would have taught or suggested that any of the excipients in the long list provided therein would be better than others (*i.e.*, would be a "lead"), and the Office Action fails to provide otherwise. Likewise, with regard to the new claim 61, there is no disclosure in Zeldis that having pomalidomide at the specific mass percent range recited by the presently amended claims in combination with the specific binders and fillers, would result in compositions with advantageous properties. Therefore, those skilled in the art would not have been able to reasonably expect, based on Zeldis' disclosure, that the claimed oral dosage forms would possess particularly useful properties, and thus, would not have been prompted or guided to make and use the claimed oral dosage forms. Accordingly, Applicants respectfully point out that no *prima facie* case of obviousness is established by the Office Action, and thus, the rejection should be withdrawn for this reason alone.

Furthermore, even assuming, *arguendo*, that a person of ordinary skill in the art would have have been somehow guided to oral dosage forms comprising pomalidomide and excipients such as mannitol and pre-gelatinized starch, the unexpected results disclosed in the specification would rebut any *prima facie* case of obviousness that may have been established by Zeldis. (*See In re*

May, 574 F.2d 1082, 1094 (C.C.P.A. 1978) (unexpected results rebut a *prima facie* case of obviousness); MPEP § 2145 and 716.02(a)). In this regard, it is clearly provided in the current specification that the claimed oral dosage forms have been advantageously found to have stability adequate for clinical and other uses. (*See* Specification, pages 42-43). The stability shown for the claimed dosage forms would have been unexpected in view of the fact that those skilled in the art would have completely lacked any expectation, in particular based on Zeldis' disclosure, as to what specific excipients, at what amount levels, would bring about any advantageous properties in combination with Pomalidomide. For at least the reasons above, Applicants respectfully request that the rejection of the claims be withdrawn.

On pages 7-10 of the Office Action, the Examiner rejects claims 8-10, 18-20, 28, 38-40, 48-50, and 58-60, are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Zeldis as applied to claims 1-4, 7, 11-14, 17, 21-24, 27, 31-34, 37, 41-44, 47, 51-54 and 57, in view of Remington's Pharmaceutical Sciences, 17th Edition, published 1985, pages 1613-1615 and 1625-1626 ("Remington"). Specifically, the Examiner alleges that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have combined the bined the dosage forms in Zeldis with the teachings of Remington. Applicants respectfully traverse this rejection.

As discussed above, Zeldis does not teach or suggest the advantages of the specific oral dosage forms claimed in the current application. While Remington generally teaches methods of preparing various oral dosage forms (*i.e.* tablets, capsules), it also does not teach or suggest anything with regard to the advantages of the specific dosage forms claimed herein. Applicants submit that Remington does not add any substance to the rejections, and thus, the combination of Zeldis and Remington still do not teach or suggest the presently claimed dosage forms. For this reason, Applicants respectfully request that the rejection be withdrawn.

On pages 10-11 of the Office Action, the Examiner rejects claims 5, 6, 15, 16, 25, 26, 35, 36, 45, 46, 55, and 56 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Zeldis as applied to claims 1-4, 7, 11-14, 17, 21-24, 27, 31-34, 37, 41-44, 47, 51-54 and 57 in view of McNally *et al.* U.S. Patent No. 5,593,696 ("McNally"). The Examiner alleges it would have been obvious to a person of ordinary skill in the are at the time of the invention to have modified the dosage forms taught by Zeldis by using sodium stearyl fumarate as taught by McNally. Applicants traverse this rejection.

Again, although Zeldis teaches the incorporation of lubricants, Zeldis does not teach or suggest the advantages of the specific oral dosage forms claimed in the immediate application. Furthermore, McNally merely rectites the use of a lubricant selected from magnesium stearate, talc, stearic acid, calcium stearate, zinc stearate, stearic acid, hydrogenated vegetable oil, leucine, glycerides, and sodium stearyl fumarate in stabilized compositions of famotidine and sucralfate and does not teach or suggest, either alone or in combination with Zeldis, any of the advantages of the claimed oral dosage forms. Therefore, the combination of references relied upon by the Examiner do not render the instant claims *prima facie* obvious and the rejection to the claims should be withdrawn.

D. Conclusion

For at least the reasons discussed above, Applicants respectfully submit that all of the pending claims are in allowable form, and thus respectfully request that their rejections be withdrawn.

A fee of $150 for a one month extention of time is believed to be due with this paper. If any additional fees are required for the submission of this paper, or to avoid abandonment of this application, please charge such fees to Jones Day Deposit Account No. 503013 (referencing 501872-999831).

Respectfully submitted,

Date: August 16, 2012

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